Journal of Cardiology 65 (2015) 390–396

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Associations between different types of hypoglycemic agents and the clinical outcome of percutaneous coronary intervention in diabetic patients—From the FU-Registry

Amane Ike (MD, PhD)[a,1], Kazuyuki Shirai (MD, PhD)[b,1], Hiroaki Nishikawa (MD, PhD)[a,1], Atushi Iwata (MD, PhD)[a,1], Eiji Yahiro (MD, PhD)[a], Makoto Sugihara (MD, PhD)[a], Akira Kawamura (MD, PhD)[a], Yoshinari Uehara (MD, FJCC)[a], Bo Zhang (PhD)[c], Masahiro Ogawa (MD, PhD)[a], Ken Mori (MD)[d], Shin-ichiro Miura (MD, PhD, FJCC)[a], Keijiro Saku (MD, PhD, FACP, FACC, FJCC)[a,*]

[a] Department of Cardiology, Fukuoka University School of Medicine, Fukuoka, Japan
[b] Division of Cardiology, Hakujyuji Hospital, Fukuoka, Japan
[c] Department of Biochemistry, Fukuoka University School of Medicine, Fukuoka, Japan
[d] Department of Cardiology, Fukuoka University Chikushi Hospital, Fukuoka, Japan

ARTICLE INFO

Article history:
Received 27 September 2013
Received in revised form 29 May 2014
Accepted 20 June 2014
Available online 12 August 2014

Keywords:
Clinical outcome
Diabetes mellitus
Hypoglycemic agents
Insulin therapy
Percutaneous coronary intervention

ABSTRACT

Background: It is not clear whether it is reasonable to use particular drugs for glycemic control in preference to other hypoglycemic agents in terms of the clinical outcome of percutaneous coronary intervention (PCI) in patients with diabetes mellitus (DM).

Methods and results: Among 2148 patients (2568 lesions) in the FU-Registry, DM patients who underwent PCI ($n = 758$; 922 lesions) were investigated to clarify the effects of various drugs for glycemic control on the clinical outcome [major adverse cardiac events (MACEs): death, myocardial infarction (MI), and target lesion revascularization (TLR)] over approximately 300 days of follow-up (UMIN000005679). The MACEs(+) group ($n = 165$) had a higher usage of insulin ($p < 0.001$) and a lower usage of biguanides (BG, $p < 0.05$) and dipeptidyl peptidase-IV inhibitors ($p < 0.05$) at PCI, compared to the MACEs(−) group ($n = 593$). A multivariate logistic regression analysis showed that low-density lipoprotein cholesterol, insulin use, atherosclerosis obliterans, and lesion reference might be significantly associated with MACEs, while BG use was negatively correlated with MACEs ($p = 0.04$). The cumulative frequency of MACEs in the insulin-treated group was significantly higher ($p < 0.05$) than that in the non-insulin group, and the strongest association between insulin with MACEs was seen in the hemoglobin (Hb) A1c 6.5–7.5% group. There tended to be a negative correlation between the use of insulin and MACEs, with risk ratios of <1, for the HbA1c >8.5% groups.

Conclusions: Among different hypoglycemic agents, treatment with insulin was associated with poor mid-term clinical outcomes in DM patients who underwent PCI, while BG use was negatively correlated with MACEs. It may be reasonable for patients with HbA1c >8.5% to avoid hyperglycemia and glucotoxicity, even through the use of insulin.

Introduction

Percutaneous coronary intervention (PCI) in diabetes mellitus (DM) patients is associated with higher rates of stent restenosis and major adverse cardiovascular events (MACEs) compared to PCI in non-DM patients, and both the short- and long-term outcomes of treatment are poor [1–4]. Impairment of the vascular

Abbreviations: PCI, percutaneous coronary intervention; MACEs, major adverse cardiac events; TLR, target lesion revascularization.

* Corresponding author at: Department of Cardiology, Fukuoka University School of Medicine, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan. Tel.: +81 92 801 1011; fax: +81 92 865 2692.
E-mail address: saku-k@fukuoka-u.ac.jp (K. Saku).

[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.jjcc.2014.06.012
0914-5087/

endothelium [5] by chronic hyperglycemia, which magnifies the inflammatory response [6] and accelerates cellular proliferation [7], and the existence of pathological conditions that aggravate vascular impairment, such as accentuation of the blood coagulation system [8], have been reported to be the causative factors, and this remains a problem despite the emergence of the drug-eluting stent (DES) and a decline in stent restenosis [9].

Although suppression of the onset of cardiovascular disease (CVD) in the long-term by proactive glycemic control using insulin and sulfonylurea (SU) agents has been established, as proven by studies such as UKPDS 80 [10], the Framingham Study [11], and DCCT/EDIC [12], there has been no difference in the incidence of cardiovascular events during follow-up periods of <10 years [13,14]. In a previous report, we showed that proactive glycemic control initiated at the time of PCI does not improve the clinical outcome of PCI in the mid-term [4]. However, due to the design of the study, many points regarding the association between the hypoglycemic agents and the clinical outcome were not clear. In addition, it is not clear whether it would be better to use any particular drugs for glycemic control in preference to other hypoglycemic agents including insulin, in terms of the clinical outcome of PCI in DM patients. Therefore, we compared mid-term clinical outcomes, including angiographic analyses, at an average of 9 months after PCI in DM patients who were divided into MACEs(+) and MACEs(−) groups, to clarify the association between the use of hypoglycemic agents and outcome.

Methods

Patients

The FU-Registry was established in 2003 and combines PCI data from the Fukuoka University Hospital Group. We performed an angiographical analysis using the database from the FU-Registry [UMIN000005679, Fukuoka University Hospital EC/IRB: 10-1-08(09-105)].

Patients with DM were extracted from among the total 2148 patients (2568 lesions) in whom PCI was performed during the period from January 2003 to July 2012 at Fukuoka University Hospital, Fukuoka University Chikushi Hospital, and Hakujyuji Hospital in Fukuoka. The comparisons were made by first excluding patients with non-DM, acute coronary syndrome (ACS), and hemodialysis (HD), and then dividing the remaining 758 cases (922 lesions) into a MACEs(−) group (593 cases; 754 lesions) and a MACEs(+) group (165 cases; 168 lesions) (Fig. 1). The average follow-up period was 300 days, clinical follow-up was carried out in all cases, and the presence or absence of MACEs was confirmed at the last outpatient visit, or by telephone interview in some cases. Angiographic follow-up was performed for approximately 95% of the full cohort. Patients were considered to have DM if any of the diagnostic criteria defined by the Japan Diabetes Society [fasting blood sugar level ≥ 126 mg/dl, 2-h 75 g oral glucose tolerance test (OGTT) glucose level ≥ 200 mg/dl or random blood sugar level ≥ 200 mg/dl (venous plasma levels)] were met, or if they continued the oral administration of hypoglycemic drugs with a clear diagnosis of DM, as described previously [4].

Measurements and definitions

The hemoglobin (Hb) A1c value was evaluated according to the US National Glycohemoglobin Standardization Program (NGSP) [15]. MACEs were defined to include three outcomes: all deaths, myocardial infarction (MI), and target lesion revascularization (TLR). MI included both ST elevation MI and non-ST elevation MI, either with clear ischemic electrocardiographic changes or with elevated cardiogenic enzymes [positive rapid troponin T, creatine kinase (CK) greater than double the reference level, CK-MB greater than the upper limit of the reference levels]. Stent thrombosis was considered to include definite, probable, and possible according to the definition of the ARC (Academic Research Consortium) [16].

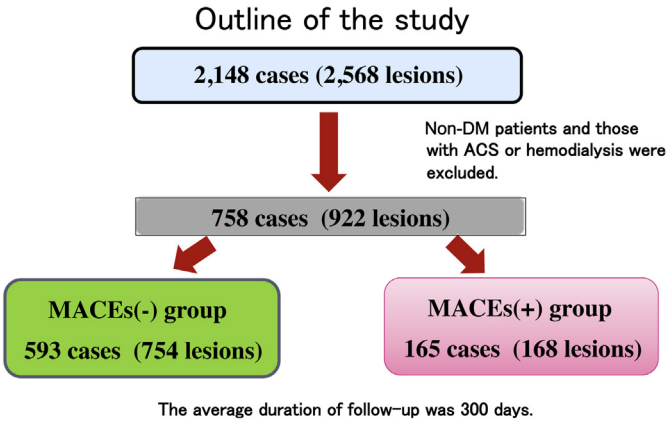


Fig. 1. Outline of the study (the FU-Registry). MACEs were defined to include three outcomes: all deaths, myocardial infarction, and target lesion revascularization. ACS, acute coronary syndrome; MACEs, major adverse cardiovascular event.

PCI intravascular ultrasound procedure

PCI was performed in cases in which there was >50% stenosis angiographically with either chest symptoms or proof of ischemia by non-invasive tests (treadmill stress electrocardiogram, myocardial scintigraphy). The end-point of the technique was the absence of any dissection resulting in the obstruction of blood flow, achievement of thrombolysis in MI III flow and <10% stenosis angiographically. The decision to perform intravascular ultrasound (IVUS) was made by the cardiologists, and it was performed in approximately 1/3 of all cases. With regard to pre-procedural IVUS, cases in which lesions were not crossed were not included in the present analysis and only the results of post-procedural IVUS measurements were used.

Medication (antiplatelets)

With regard to antiplatelet agents, in all cases, aspirin and either ticlopidine 200 mg or clopidogrel 75 mg were started at least 48 h before stent insertion. In principle, in cases with a bare-metal stent (BMS), antiplatelet agents other than aspirin were continued for at least 2 weeks, and in cases with a DES, all antiplatelet agents were administered for at least 9 months after PCI. Insulin included different types of insulin, and thiazolidine (pioglitazone), dipeptidyl peptidase (DPP)-IV inhibitors (sitagliptin, vildagliptin, alogliptin), Sulfonylureas (SU; gliclazide, glibenclamide, glimepiride), biguanides (BG; metformin hydrochloride), and α-glucosidase inhibitor (α-GI; acarbose, voglibose, miglitol) were mostly used in this registry.

Quantitative coronary angiography

Quantitative coronary angiography (QCA) was carried out randomly in approximately 70% of all cases. Quantitative and qualitative analyses were made at the core laboratory of Fukuoka University, using CMS-GFT (MEDIS, Leiden, The Netherlands), as described previously [4,17,18]. Analyses were made for pre-procedural, post-procedural, and follow-up angiograms. All measurements were made using images after the intracoronary injection of nitroglycerin. Segments were defined as in-stent, the

proximal edge of the stent, and 5 mm from the distal edge of the stent. Late-loss was defined as the difference between the minimum lesion diameter (MLD) in the post-procedural angiogram and the MLD in the follow-up angiogram. In addition, restenosis was defined as >50% stenosis.

Statistical analysis

Statistical analysis was carried out at the University of Fukuoka using SAS software (Version 9.1, SAS Institute, Cary, NC, USA). The chi-square test was used for comparisons of categorical variables between groups. The Wilcoxon rank sum test and the Student's *t*-test were used for comparisons of continuous variables between groups shown as the mean ± SD. The multiple logistic regression analysis was used to examine the independent association between variables of patient and lesion characteristics and MACEs [19]. To examine the independent association between variables of patient characteristics and MACEs, conventional risk factors of CVD, including age, gender, body mass index (BMI), and hypertension, and variables of patient characteristics that were associated with MACEs in the univariate analysis, including serum lipids, HbA1c, and hypoglycemic agents, were included in the regression model. To examine the independent association between variables of lesion characteristics, variables of lesion characteristics that were associated with MACEs in the univariate analysis were included in the regression model. For variables that were strongly correlated, only one variable was included in the model to avoid multicollinearity. The cumulative frequency of MACEs for each follow-up period in patients with and without insulin use was calculated as the percentage of the number of patients who had MACEs during that period in total number of patients in each group, respectively. The association between insulin use and MACEs after controlling follow-up period was assessed by Cochran–Mantel–Haenszel test [19]. A p value <0.05 was considered to be statistically significant.

Results

Factors that most strongly predict MACEs after PCI

With regard to follow-up clinical outcomes of MACEs in this registry, the incidence of TLR-PCI, TLR-coronary artery bypass graft (CABG), MI, and death were 85.4%, 4.2%, 10.9%, and 9.1%, respectively. Table 1 shows the patient characteristics in the MACEs(+) and MACEs(−) groups. The MACEs(+) group included more males ($p < 0.05$), and showed higher levels of low-density lipoprotein cholesterol (LDL-C) ($p < 0.001$), non-high-density lipoprotein cholesterol (non-HDL-C) ($p < 0.01$), and lower HDL-C levels at PCI and at the 9-month to 1-year follow-up. The MACEs(+) group was also more likely to have had prior PCI ($p < 0.01$) and atherosclerosis obliterans (ASO) ($p < 0.001$), and less hypertension ($p < 0.05$). The MACEs(+) group showed a higher frequency of prior in-stent restenosis ($p < 0.05$) and a lower use of a DES ($p < 0.05$). In addition, the lesion length was greater ($p < 0.05$) and the reference diameter was smaller ($p < 0.01$) in the MACEs(+) group, while post-procedural IVUS parameters were significantly smaller in the MACEs(+) compared to MACEs(−) group, except lesion % plaque (Table 1).

Association between the hypoglycemic agents used and MACEs

Table 2 shows the hypoglycemic drugs used. The MACEs(+) group was more likely to be receiving insulin therapy ($p < 0.001$) and less likely to be receiving BG ($p < 0.01$) or DPP-IV inhibitors ($p < 0.05$), at both the PCI procedure and the follow-up periods (over approximately 300 days).

Table 1
Patient and lesion characteristics in the MACEs(+) and MACEs(−) groups.

	MACEs(−) group $N = 593$	MACEs(+) group $N = 165$
Patient characteristics		
Mean age (year)	67.9 ± 9.7	68.1 ± 9.8
Gender (male) (%)	70.6	79.9*
BMI (kg/m^2)	24.1 ± 3.5	24.2 ± 3.0
UCG-LVEF (%)	61.6	60.6
Blood sampling test at PCI procedure		
Cr (mg/dl)	1.00 ± 0.49	1.02 ± 0.40
TC (mg/dl)	179.9 ± 39.2	188.6 ± 45.7*
TG (mg/dl)	141.3 ± 94.7	134.8 ± 71.2
HDL-C (mg/dl)	48.3 ± 12.7	46.5 ± 11.8
LDL-C (mg/dl)	102.8 ± 33.9	115.5 ± 39.9‡
Non-HDL-C (mg/dl)	131.9 ± 37.9	142.8 ± 45.8†
LDL-C/HDL-C	2.3	2.7‡
HbA1c (%)	7.0 ± 1.2	7.1 ± 1.3
Follow-up data		
BMI (kg/m^2)	24.2 ± 3.8	24.5 ± 3.2
Blood sampling test at follow-up		
TC (mg/dl)	170.5 ± 39.5	178.5 ± 37.2*
TG (mg/dl)	143.3 ± 141.6	132.8 ± 67.9
HDL-C (mg/dl)	50.6 ± 13.1	48.0 ± 12.6*
LDL-C (mg/dl)	90.1 ± 29.2	103.8 ± 33.9‡
Non-HDL-C (mg/dl)	119.5 ± 39.7	131.6 ± 37.3†
LDL-C/HDL-C	1.9	2.4‡
HbA1c (%)	6.9 ± 1.3	6.9 ± 1.2
Prior diseases/complicated diseases		
Prior MI (%)	25.6	29.7
Prior PCI (%)	45.4	59.4†
Prior CABG (%)	5.1	7.3
ASO (%)	9.4	20.6‡
Hypertension (%)	80.8	73.9*
Hyperlipidemia (%)	77.2	70.3
Medications at PCI procedure		
Ca blockers (%)	53.8	47.9
ACEIs (%)	13.2	15.1
β-Blockers (%)	11.5	15.8
Statins (%)	74.4	76.4
ARBs (%)	67.5	73.3
	$N = 754$	$N = 168$
Lesion characteristics		
3 vessel disease (%)	47.1	41.1
RCA/LAD/CX (%)	30.7/46.2/17.2	30.1/52.2/15.4
LMT lesion (%)	3.3	1.9
Prior in stent restenosis (%)	15.1	35.7†
AHA/ACC type B2 + C (%)	61.1	63.7
Severe calcification (%)	12.3	13.3
Drug eluting stent (%)	64.5	58.3*
QCA	$N = 594$	$N = 117$
Pre-procedural results		
Lesion length (mm)	18.4 ± 10.1	21.5 ± 12.9*
Reference diameter (mm)	2.6 ± 0.6	2.4 ± 0.6†
MLD (mm)	0.8 ± 0.4	0.7 ± 0.4
%DS (%)	71.1	70.9
Post-procedural results		
MLD (mm)	2.0 ± 0.6	1.9 ± 0.6
%DS (%)	24.6	25.2
Stent length (mm)	22.7 ± 11.5	25.5 ± 13.6
Stent MLD (mm)	2.5 ± 0.5	2.4 ± 0.5
Stent reference (mm)	2.8 ± 0.5	2.8 ± 0.4
Stent %DS (%)	11.4	14.5
	$N = 244$	$N = 69$
IVUS (post-procedural results)		
Lesion EEM CSA (mm^2)	14.1 ± 5.0	12.5 ± 4.3†
Lesion lumen CSA (mm^2)	6.4 ± 2.5	5.7 ± 1.8†
Lesion atheroma CSA (mm^2)	7.7 ± 3.3	6.8 ± 3.4*

Table 1 (*Continued*)

	N = 244	N = 69
Lesion % plaque (%)	53.8	54.1
Minimum stent CSA (mm^2)	6.6 ± 3.2	5.8 ± 1.8†

BMI: body mass index, UCG LVEF: ultrasound cardiography left ventricle ejection fraction, Cr: creatinine, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, Non-HDL-C: non high density lipoprotein cholesterol, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, ASO: arteriosclerosis obliterans, ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin II receptor blockers, RCA: right coronary artery, LAD: left anterior descending coronary artery, CX: left circumflex coronary artery, LMT: left main trunk, MLD: minimum lumen diameter, %DS: percent diameter stenosis, CSA: cross sectional area, EEM: external elastic membrane.
* $p < 0.05$.
† $p < 0.01$.
‡ $p < 0.001$.

Table 2
Hypoglycemic agents used in the MACEs(+) and MACEs(−) groups.

	MACEs(−) group	MACEs(+) group
Medications for DM at procedure		
Sulfonylurea (%)	31.9	25.5
α-GIs (%)	21.4	21.8
Thiazolidines (%)	11.6	13.3
Insulin (%)	27.8	40.0‡
Biguanides (%)	8.3	3.6*
DPP-IV inhibitors (%)	8.8	2.4*
Medication for DM at follow-up		
Sulfonylurea (%)	32.5	29.7
α-GIs (%)	21.4	16.9
Thiazolidines (%)	13.0	13.3
Insulin (%)	19.6	38.9‡
Biguanides (%)	10.1	9.0
DPP-IV inhibitors (%)	10.6	5.4*

α-GI, α-glucosidase inhibitor.
* $p < 0.05$.
‡ $p < 0.001$.

Table 3
Multivariate logistic regression analysis of the association between variables of patient and lesion characteristics and MACEs.

	p value	Odds ratio (95% CI)
Patient characteristics of pre-procedural		
Age	0.46	1.01 (0.99–1.03)
BMI	0.99	1.04 (0.94–1.05)
Gender	0.70	1.10 (0.68–1.81)
HDL-C	0.06	0.98 (0.97–1.00)
LDL-C	0.003	1.01 (1.01–1.02)
HbA1c	0.28	0.91 (0.76–1.08)
Insulin	0.007	1.87 (1.19–2.93)
Biguanides	0.06	0.44 (0.09–1.02)
Sulfonylurea	0.46	0.83 (0.50–1.35)
DPP-IV inhibitors	0.12	0.30 (0.10–1.47)
Prior PCI	0.05	1.68 (0.99–2.53)
ASO	0.001	2.31 (1.38–3.87)
Hypertension	0.29	0.77 (0.47–1.26)
Lesion characteristics		
Drug eluting stent	0.97	1.00 (0.92–1.09)
Prior in-stent restenosis	0.11	2.14 (0.81–5.51)
Lesion length	0.41	1.50 (0.59–4.18)
Lesion references (pre-procedural results)	0.01	0.28 (0.10–0.68)
Lesion EEM CSA	0.54	1.09 (0.84–1.52)
Lesion atherome CSA	0.26	0.81 (0.54–1.15)
Stent minimum CSA	0.80	1.02 (0.76–1.17)

BMI, body mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; ASO, arteriosclerosis obliterans; CSA, cross-sectional area; EEM, external elastic membrane; CSA, cross-sectional area.

Clinical and angiographic backgrounds of insulin users [Insulin(+) group] and non-insulin users [Insulin(−) group] among patients with MACEs

The clinical characteristics, including gender, BMI, left ventricular ejection fraction, blood examinations at PCI procedure and at follow-up, prior MI, prior CABG, etc., were all similar between the groups, while there were differences in ASO and lesion references (mm) in pre-procedural QCA, i.e. the Insulin(+) group had a higher incidence of ASO (19.5% vs. 10.4%, $p < 0.01$), while the lesion references (mm) in pre-procedural QCA were shorter (2.4 ± 0.6 mm vs. 2.6 ± 0.6 mm, $p < 0.01$), compared to the Insulin(−) group (data not tabulated).

Multivariate logistic regression analysis

Table 3 shows the results of a multivariate logistic regression analysis of the patient and lesion characteristics and MACEs(+). LDL-C ($p = 0.003$), insulin use ($p = 0.007$), ASO ($p = 0.001$), and the lesion reference ($p = 0.01$) were significantly associated with MACEs(+). Only hypoglycemic agents were extracted to examine their relationship to MACEs by multivariate logistic regression analysis, and, as expected, insulin use showed a strong positive correlation with MACEs [odds ratio: 1.58 (95% CI: 1.06–2.37), $p = 0.02$]. On the other hand, BG use showed a negative correlation with MACEs [odds ratio: 0.34 (95% CI: 0.1–0.87), $p = 0.04$] (Fig. 2A and B). While the odds ratio for DPP-IV inhibitors was below 1.0, this result was not significant (Fig. 2A and B).

Effects of insulin use on the cumulative frequency of MACEs

The effects of insulin use on the cumulative frequency of MACEs are shown in Fig. 3. Insulin use was associated with an increase in MACEs as follow-up period increased ($p = 0.005$).

Association of insulin use with MACEs according to the value of HbA1c

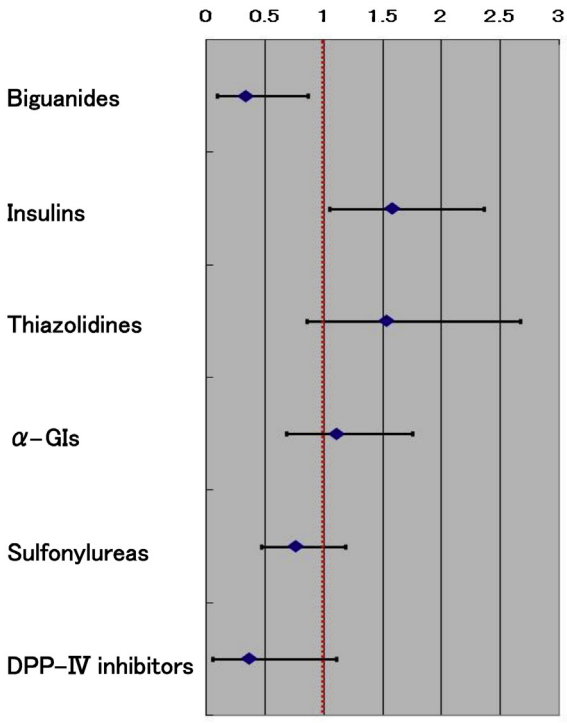
The entire cohort of 758 DM cases in the present study was further stratified according to the HbA1c value at PCI into a <6.5% group (148 cases), 6.5–7.5% group (218 cases), 7.5–8.5% group (125 cases), 8.5–9.5% group (65 cases), and >9.5% group (49 cases), and the association between insulin and MACEs was studied in each group (Fig. 4). As a result, the strongest association between insulin and MACEs was seen in the HbA1c 6.5–7.5% group ($p < 0.0001$, odds ratio: 3.23, 95% CI: 1.6–6.5).

In addition, in the other groups, although there were no significant differences, there tended to be a negative correlation between the use of insulin and MACEs, with odds ratios of <1 for the HbA1c 8.5–9.5% and >9.5% groups.

Discussion

There have been many reports, such as UKPDS 80 [10] and DCCT/EDIC [12], on the suppressive effect of proactive glycemic control by consolidation therapy, including insulin, on cardiovascular events in the long term (more than a decade). However, studies such as DCCT [14] and UKPDS [13] have reported that, although microangiopathy was significantly suppressed in a consolidation therapy group, no difference was found in the incidence of cardiovascular events between a consolidation therapy group and an ordinary therapy group. Further, in the ACCORD trial [20], while follow-up was discontinued after 3.5 years because of an increase in total deaths, there was no difference in the incidence of cardiovascular events between the consolidation therapy group and the ordinary therapy group. Based on these reports, it is reasonable to consider that appropriate

A



B

	Odds ratio (95%CI)	P value
Biguanides	0.34 (0.1–0.87)	0.04
Insulins	1.58 (1.06–2.37)	0.02
Thiazolidines	1.54 (0.86–2.68)	0.13
α−GIs	1.11 (0.69–1.76)	0.66
Sulfonylureas	0.76 (0.48–1.19)	0.23
DPP−IV inhibitors	0.37 (0.06–1.28)	0.17

α-GIs, α-glucosidase inhibitors

Fig. 2. (A) and (B) The relationship between hypoglycemic agents and major adverse cardiovascular events was examined by a multivariate logistic regression analysis (only hypoglycemic agents were extracted), after adjusting for confounding variables. α-GI, α-glucosidase inhibitor; DPP, dipeptidyl peptidase.

consolidation therapy, without hypoglycemia, reduces the incidence of cardiovascular events in the long term and the incidence of microangiopathy in the short term.

In our study, BG ($p = 0.04$), SU (ns) and DPPIV inhibitors ($p = 0.17$) were tend to be associated with a lower incidence of MACEs (Fig. 2A and B), while insulin ($p = 0.02$), thiazolidines ($p = 0.13$), and α-GI ($p = 0.66$) were shown to promote MACEs. Since Tables 2 and 3 and Fig. 2A and B showed that insulin use was a major cause of MACEs, the time-line of cumulative MACEs was analyzed (Fig. 3). Insulin therapy was associated with an increase in MACEs in the patients overall, as follow-up period increased.

Insulin is thought to have both an atherosclerosis-suppressive effect and an atherosclerosis-inducing effect, and it is not clear how the physiological effect of insulin is involved in the results of the aforementioned large-scale trials. The atherosclerosis-suppressive effects of insulin include activation of the mechanism of NO production in vascular endothelial cells [21–23] which, through NO, is thought to promote vasorelaxation, the inhibition of platelet

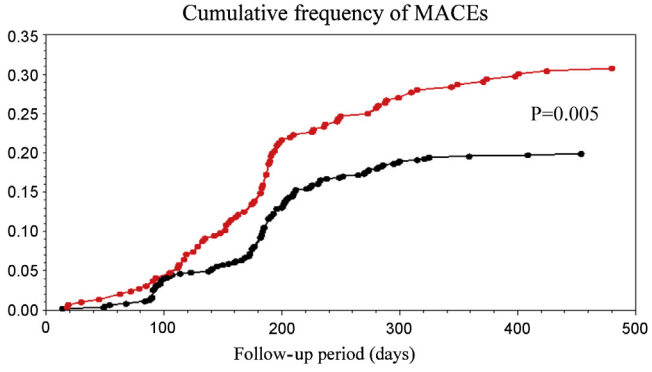


Fig. 3. The cumulative frequency of major adverse cardiovascular events (MACEs) in the overall patients with Insulin(+) (red) and Insulin(−) (black). The cumulative frequency of MACEs for each follow-up period in patients with and without insulin use was calculated as the percentage of the number of patients who had MACEs during that period in total number of patients in each group, respectively. The association between insulin use and MACEs after controlling follow-up period was assessed by Cochran–Mantel–Haenszel test [19].

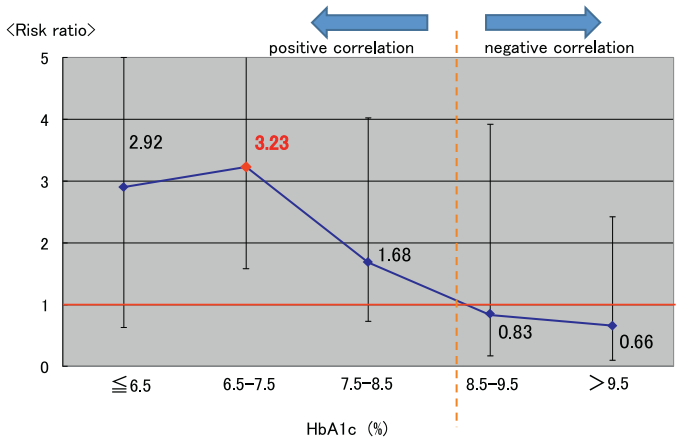


Fig. 4. The association of insulin use with major adverse cardiovascular events according to the value of hemoglobin (Hb) A1c. Positive and negative correlations were observed at below and above an HbA1c value of 8.5%, respectively.

aggregation and inhibition of the proliferation of vascular smooth muscle. The atherosclerosis-inducing effects include accentuation of the renin–angiotensin system [24] and platelet activity as well as the direct proliferation of smooth muscle cells [25,26] through the activity of the sympathetic nervous system [27]. A recent report that considered the initiation of insulin rather than the addition of another oral glucose-lowering drug to double or triple oral therapy did not show a significant increase in vascular events [28]. A single bedtime dose of insulin was reported to be safe and effective, and did not influence in-stent restenosis [29]. Therefore, atherosclerosis-suppressive and atherosclerosis-inducing effects are counterbalanced in the human body.

The standard use of stents at PCI and insulin therapy have changed over time, and the long study period have affected the results. However, in the present study, lesion stent late loss, which represents the degree of neointimal proliferation, in the Insulin(+) group was significantly greater than that in the Insulin(−) group (0.45 ± 0.72 mm vs. 0.27 ± 0.66 mm, respectively, data not tabulated), despite similar patient and lesion characteristics and similar usage rates of DES (around 60%), to result in a higher in-stent restenosis rate (35.4% vs. 21.3%, respectively).

The incidences of MI and stent thrombosis were also significantly higher in the Insulin(+) group. While the details of the occurrence of hypoglycemia are not clear, there was no difference between the mortality rates in the two groups. In the multivariate analysis (Table 3), insulin showed the second strongest association with MACEs after ASO, suggesting that the atherosclerosis-inducing effect of insulin is stronger than the atherosclerosis-suppressive effect in the area where PCI has been performed. However, these results do not allow us to conclusively state whether it is better to not use insulin for patients in whom PCI is performed.

The strongest association between insulin with MACEs was seen in the HbA1c 6.5–7.5% group. In the HbA1c 8.5–9.5% and over 9.5% groups, the use of insulin might be associated with lower incidences of MACEs (Fig. 4). Therefore, in patients who have undergone PCI, it may be beneficial to introduce insulin therapy for HbA1c values >8.5%.

Oral DPP-IV inhibitors have also been shown to provide reasonable reductions in HbA1c along with other oral glucose-lowering drugs, raise levels of the incretin glucagon-like peptide-1 (GLP-1), and inhibit the release of glucagon [30,31]. They have been shown to improve endothelial function through anti-inflammatory effects, beyond their hypoglycemic action [32]. In our study, use of DPP-IV inhibitors and BG in MACEs(+) were lower than those in MACEs(−) at PCI, albeit this effect was not statistically significant by a multivariate logistic regression analysis. During insulin therapy, we should seek to improve the constitution of DM patients, and ultimately should seek to discontinue treatment with insulin due to improved insulin sensitivity. This approach may be associated with an improvement in the mid-term clinical outcomes of DM patients who undergo PCI. In this context, the use of a new DPP-IV inhibitor may be useful for DM patients who undergo PCI.

Limitations

The present study was not a prospective cohort study and included patients in whom PCI was performed from 2003 to 2012. Insulin levels were not measured, and we did not collect detailed DM data, such as information regarding blood sugar control before PCI and the medical history of DM (such as how long the patients had had DM and the number of years they had been treated). Information regarding the amounts or types of insulin used in the present study was not clear, and thus we could not examine the effects of these factors.

Conclusion

Among different hypoglycemic agents, treatment with insulin was associated with poor mid-term clinical outcomes in DM patients who underwent PCI, while the use of BG was negatively correlated with MACEs. Since the use of insulin was associated with a lower incidence of MACEs in patients with HbA1c >8.5%, it may be beneficial to control hyperglycemia in these patients even with the use of insulin.

Disclosure

Research and education grants, consulting, and promotional speaking (YU, SM, KS) from MSD Co., SANOFI, Takeda Pharmaceutical Co., Ltd., Bayer, Eli Lilly Co. (clinical research grant), and TOA EIYO Co., and KS and SM are Directors of ^{NPO} Clinical and Applied Science, Fukuoka, Japan. Kaz Sh, SM, KS had a grant from the Public Interest Incorporated Foundation of "Clinical Research Promotion Foundation" in Fukuoka, Japan, and the part of work was transferred into ^{NPO} Clinical and Applied Science, Fukuoka, Japan. KS has Endowed Department of Molecular Cardiovascular Therapeutics (YU, SM), Fukuoka University, supported by MSD Co., Ltd., Tokyo, Japan, and Endowed Department of Community and Emergency Medicine (HN, MS), Fukuoka University, supported by Izumi City, Kagoshima, Japan.

Acknowledgments

This work was supported by research grants from the Central Research Institute of Fukuoka University (2008–2012), the FU-Global Program (2008–2010), the AIG Collaborative Research Institute of Cardiovascular Medicine, Fukuoka University (2011–2013), Endowed Department of Molecular Cardiovascular Therapeutics, Fukuoka University, and Endowed Department of Community and Emergency Medicine, Fukuoka University.

References

[1] Flaherty JD, Davidson CJ. Diabetes and coronary revascularization. JAMA 2005;293:1501–8.
[2] Cutlip DE, Chhabra AG, Baim DS, Chauhan MS, Marulkar S, Massaro J, Bakhai A, Cohen DJ, Kuntz RE, Ho KK. Beyond restenosis: five-year clinical outcomes from second-generation coronary stent trials. Circulation 2004;110:1226–30.
[3] Lee TT, Feinberg L, Baim DS, Holmes DR, Aroesty JM, Carrozza Jr JP, Cohen DJ, Ho KK, Cutlip DE. Effect of diabetes mellitus on five-year clinical outcomes after single-vessel coronary stenting (a pooled analysis of coronary stent clinical trials). Am J Cardiol 2006;98:718–21.
[4] Ike A, Nishikawa H, Shirai K, Mori K, Kuwano T, Fukuda Y, Takamiya Y, Yanagi D, Kubota K, Tsuchiya Y, Zhang B, Miura S, Saku K. Impact of glycemic control on the clinical outcome in diabetic patients with percutaneous coronary intervention – from the FU-registry. Circ J 2011;75:791–9.
[5] Stehouwer CD, Lambert J, Donker AJ, van Hinsbergh VW. Endothelial dysfunction and pathogenesis of diabetic angiopathy. Cardiovasc Res 1997;34:55–68.
[6] Farah R, Shurtz-Swirski R, Lapin O. Intensification of oxidative stress and inflammation in type 2 diabetes despite antihyperglycemic treatment. Cardiovasc Diabetol 2008;7:20.
[7] Tchaikovski V, Olieslagers S, Bohmer FD, Waltenberger J. Diabetes mellitus activates signal transduction pathways resulting in vascular endothelial growth factor resistance of human monocytes. Circulation 2009;120:150–9.
[8] McBane 2nd RD, Hardison RM, Sobel BE. Comparison of plasminogen activator inhibitor-1, tissue type plasminogen activator antigen, fibrinogen, and D-dimer levels in various age decades in patients with type 2 diabetes mellitus and stable coronary artery disease (from the BARI 2D trial). Am J Cardiol 2010;105:17–24.
[9] Airoldi F, Briguori C, Iakovou I, Stankovic G, Biondi-Zoccai G, Carlino M, Chieffo A, Montorfano M, Cosgrave J, Michev I, Rogacka R, Sangiorgi GM, Colombo A. Comparison of sirolimus versus paclitaxel eluting stents for treatment of coronary in-stent restenosis. Am J Cardiol 2006;97:1182–7.
[10] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–89.
[11] Garcia MJ, McNamara PM, Gordon T, Kannel WB. Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study. Diabetes 1974;23:105–11.

[12] Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–53.
[13] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53.
[14] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–86.
[15] Japan Diabetes Society. http://www.jds.or.jp/common/fckeditor/editor/filemanager/connectors/php/transfer.php?file=/uid000025_474C323031332D636F6C756D6E2E706466 2013 [accessed 05.04.14].
[16] Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
[17] Fukuda Y, Shirai K, Miura S, Ike A, Takamiya Y, Kuwano T, Yanagi D, Mori K, Kubota K, Miller N, Nishikawa H, Zhang B, Saku K. The impact of angulated lesions on angiographic late loss in patients with drug-eluting stent implantation. J Cardiol 2009;53:396–401.
[18] Yanagi D, Shirai K, Takamiya Y, Fukuda Y, Kuwano T, Ike A, Mori K, Kubota K, Iwata A, Fujimi K, Kawamura A, Nishikawa H, Miller N, Zhang B, Tsuchiya Y, et al. Results of provisional stenting with a sirolimus-eluting stent for bifurcation lesion: multicenter study in Japan. J Cardiol 2008;51:89–94.
[19] SAS Institute Inc.. SAS Online Doc 9.2. Cary, NC, USA: SAS Institute Inc.; 2009.
[20] Gerstein HC, Miller ME, Genuth S, Ismail-Beigi F, Buse JB, Goff Jr DC, Probstfield JL, Cushman WC, Ginsberg HN, Bigger JT, Grimm Jr RH, Byington RP, Rosenberg YD, Friedewald WT. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med 2011;364:818–28.
[21] Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G, Baron AD. Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. J Clin Invest 1996;97:2601–10.
[22] Zeng G, Quon MJ. Insulin-stimulated production of nitric oxide is inhibited by wortmannin. Direct measurement in vascular endothelial cells. J Clin Invest 1996;98:894–8.
[23] Kuboki K, Jiang ZY, Takahara N, Ha SW, Igarashi M, Yamauchi T, Feener EP, Herbert TP, Rhodes CJ, King GL. Regulation of endothelial constitutive nitric oxide synthase gene expression in endothelial cells and in vivo: a specific vascular action of insulin. Circulation 2000;101:676–81.
[24] Nickenig G, Roling J, Strehlow K, Schnabel P, Bohm M. Insulin induces upregulation of vascular AT1 receptor gene expression by posttranscriptional mechanisms. Circulation 1998;98:2453–60.
[25] Goalstone ML, Leitner JW, Wall K, Dolgonos L, Rother KI, Accili D, Draznin B. Effect of insulin on farnesyltransferase. Specificity of insulin action and potentiation of nuclear effects of insulin-like growth factor-1, epidermal growth factor, and platelet-derived growth factor. J Biol Chem 1998;273:23892–96.
[26] Jiang ZY, Lin YW, Clemont A, Feener EP, Hein KD, Igarashi M, Yamauchi T, White MF, King GL. Characterization of selective resistance to insulin signaling in the vasculature of obese Zucker (fa/fa) rats. J Clin Invest 1999;104:447–57.
[27] Berne C, Fagius J, Pollare T, Hjemdahl P. The sympathetic response to euglycaemic hyperinsulinaemia. Evidence from microelectrode nerve recordings in healthy subjects. Diabetologia 1992;35:873–9.
[28] Hall GC, McMahon AD, Carroll D, Home PD. Macrovascular and microvascular outcomes after beginning of insulin versus additional oral glucose-lowering therapy in people with type 2 diabetes: an observational study. Pharmacoepidemiol Drug Saf 2012;21:305–13.
[29] Natarajan MK, Strauss BH, Rokoss M, Buller CE, Mancini GB, Xie C, Sheth TN, Goodhart D, Cohen EA, Seidelin P, Harper W, Gerstein HC. Randomized trial of insulin versus usual care in reducing restenosis after coronary intervention in patients with diabetes. The STent Restenosis And Metabolism (STREAM) study. Cardiovasc Revasc Med 2012;13:95–100.
[30] Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368:1696–705.
[31] Kolterman OG, Buse JB, Fineman MS, Gaines E, Heintz S, Bicsak TA, Taylor K, Kim D, Aisporna M, Wang Y, Baron AD. Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. J Clin Endocrinol Metab 2003;88:3082–9.
[32] Matsubara J, Sugiyama S, Akiyama E, Iwashita S, Kurokawa H, Ohba K, Maeda H, Fujisue K, Yamamoto E, Kaikita K, Hokimoto S, Jinnouchi H, Ogawa H. Dipeptidyl peptidase-4 inhibitor, sitagliptin, improves endothelial dysfunction in association with its anti-inflammatory effects in patients with coronary artery disease and uncontrolled diabetes. Circ J 2013;77: 1337–44.